

Please enter the following new claims:

A10
16. A compound according to claim 1, wherein heteroaryl is, in each case independently, imidazole, indole, isooxazole, isothiazole, furan, oxadiazole, oxazole, pyrazine, pyridazine, pyrimidine, pyridine, pyrazole, pyrrole, tetrazole, thiazole, triazole, thiophene, thiadiazole, benzimidazole, benzofuran, benzoxazole, isoquinoline, quinoline, 2-C₁₋₆ alkyl-3-amino-1,4-benzoxazine, 2-C₁₋₆-alkyl-3-keto-1,4-benzoxazine, piperidine, pyrrolidine, morpholine, thiomorpholine, hexahydroazepine, piperazine, N-methyl-piperazine, 2,6-dimethylmorpholine, phenylpiperazine or 4-(4-fluorobenzoyl)-piperidine.

Sub 01
17. A compound according to claim 1, wherein R¹¹ is thienyl.

Sub B3
18. A compound according to claim 1, wherein R⁸ and B together or R⁷ and A together, independently of each other, form a heterocycle, which is selected from the group consisting of imidazole, pyrrole, pyrazole and triazole.

REMARKS

The Rejections under 35 USC 112, second paragraph

With respect to the rejection of the terms "heterocyclic," "hetero," "heteroaryl," etc., one of skill in the art would readily understand their scopes, which are precisely defined in the claims. With respect to the location of the hetero atoms in the ring, the claims place no limitation on their position. All reasonable options are included. Heterocyclic structures are adequately defined so that one of skill in the art would understand the scope of the term. The rejected terms are thus not indefinite.

Applicants do not understand the rejection on page 5, third paragraph of the Office Action, wherein the Office Action appears to allege that the definitions of heterocyclic or heteroaryl include As, P and B atoms. All hetero definitions list the permitted hetero atoms. The alleged As, P and B are not included.

The Office Action alleges that the type of omnibus expression was rejected in *In re Wiggins*, 179 USPQ 421 (1973). The facts of *In re Wiggins* are, however different from the current facts. The terminology employed in *In re Wiggins*, was not precise. The term in question read “a saturated heterocyclic group of five to seven ring atoms, from one to two nitrogen atoms, and up to one oxygen atom.” The claim terminology was so broad that it did not even require that the heterocyclic group contain a carbon atom. The court concluded that the term was indefinite. Contrarily, in the current case, in each case when a heterocyclic group is defined in the claims, the definition makes clear that such group contains carbon atoms.

Claims 4, 5, 6, and 8 were rejected for allegedly being multiple dependent claims dependent on another multiple dependent claim. Applicants bring the Examiner’s attention to the Preliminary Amendment filed on March 19, 2001, which amended the claims to have no multiple dependencies at all.

The 37 CFR 1.141 Issue

The Office Action alleges that claim 10 does not comply with 37 CFR 1.141 because the word “different” was inserted into 37 CFR 1.141 to specify that each species had to be in a different claim.

The language of 37 CFR 1.141(a) reads as follows:

“Two or more independent and distinct inventions may not be claimed in one national application, except that more than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in one national application, provided the application also includes an allowable claim generic to all the claimed species and all the claims to species in excess of one are written in dependent form or otherwise include all the limitations of the generic claim.”

If one were to read rule 1.141 to allow only one species per claim as the reasonable number, as alleged to be the case by the Examiner, the rest of the rule would not make sense. Neither the terms “reasonable number” and “species in excess of one,” nor the requirement that the claim be in dependent form, would make sense if each species were required to be in a

different claim. The rule does not specify a number which would be reasonable. The 17 species claimed in claim 10 comply with the reasonable number requirement of 37 CFR 1.141. The Examiner has not shown otherwise.

The Rejections under 35 USC 112, first paragraph

A section 112, first paragraph, rejection was issued alleging that the heterocyclic ring expression is so broad that it causes the claim to have a potential scope of protection beyond that which is justified by the specification disclosure.

A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995)

The Examiner has given no reason to doubt the objective truth of the statements in the application, which must be relied on for enabling support. The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of Section 112 requires nothing more than objective enablement, how such a teaching is set forth, either by use of the illustrative examples or by broad terminology, is of no importance. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

The Office Action also states that applicants should, in return for a 17/20 year monopoly, be disclosing to the public that which they know as an actual demonstrated fact. Preparation of all compounds claimed is not a requirement for claiming a genus. See *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976).

Certified Translation of German Application 18944291.2

A certified translation of German Application 18944291.2 is attached.

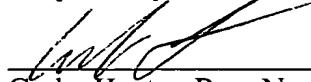
Information Disclosure Statement

Attached is an Information Disclosure Statement citing material cited in the corresponding German Search Report.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings To Show Changes Made**".

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



Csaba Henter, Reg. No. 50,908

Anthony J. Zelano, Reg. No. 27,969

Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410
Attorney Docket No.: SCH-1714A

Date: May 20, 2002
AJZ/CH/pdr/K:\Sch\1706\Reply may 2002.doc

Version With Markings To Show Changes Made

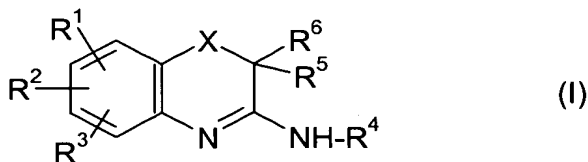
In the Abstract

The existing Abstract has been replaced with the attached new Abstract of the Disclosure, therefore no marked-up version is necessary.

In the Claims

The claims have been amended as follows:

1. (Amended) ~~Compound A~~ a compound of Formula I, ~~their~~ or a tautomeric ~~and~~ or isomeric forms ~~and~~ or a salts of a compound of Formula I.



in which wherein

X is O, ~~S~~_m ~~or~~ Se

R¹ is - (CHR⁹)_n-NR⁷-A-NR⁸-B,

R², R³, R⁴ and R⁵ is are hydrogen, ~~or~~

~~R¹ and R² together with two adjacent carbon atoms form a 5-, 6-, 7- or 8-membered ring, which is monocyclic or bicyclic, saturated or unsaturated and in which 1 or 2 CH₂-groups can be replaced by oxygen or carbonyl, and which is substituted with (CHR⁹)_f-NR⁷-A-NR⁸-B, and can be substituted with C₁₋₄-alkyl;~~

~~R³ means hydrogen, halogen, NO₂, cyano, CF₃, OCF₃, S-R⁹, O-R⁹, C₃₋₇-cycloalkyl, -NR⁹-C(=NR¹⁰)-R¹¹, -NH-CS-NR¹²R¹³, -NH-CO-NR¹²R¹³, CO-R¹⁴, NR¹⁵R¹⁶, C₆₋₁₀-aryl, which optionally is substituted with halogen, cyano, C₁₋₄-alkyl, S-R⁹, or -O-R⁹;~~

~~5- or 6-membered heteroaryl with 1 to 4 oxygen, sulfur or nitrogen atoms;~~

~~C₁₋₆-alkyl, which optionally is substituted with halogen, -OR⁹, -SR⁹, -NR¹²R¹³, =NR¹², =NOC₁₋₆-alkyl, =N-NH-aryl, phenyl, C₃₋₇-cycloalkyl or 5- or 6-membered heteroaryl;~~

~~C₂₋₆ alkynyl, which optionally is substituted with halogen, CONH₂, C≡N or phenyl,~~

R⁴ means hydrogen or acyl,

~~R⁵ and R⁶, independently of one another, mean hydrogen, C₃₋₇ cycloalkyl, phenyl, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl radicals, which can be substituted in each case with halogen, OH, O-C₁₋₆ alkyl, SH, S-C₁₋₆ alkyl, NR¹⁵R¹⁶, 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, phenyl or C₃₋₇ cycloalkyl,~~

R⁶ is methyl,

R⁷ ~~means~~ is hydrogen, C₁₋₆ alkyl, which ~~can be~~ is optionally substituted with phenyl, COOC₁₋₆ alkyl or CO-C₁₋₆ alkyl,

R⁸ ~~means~~ is hydrogen, C₁₋₆ alkyl, which ~~can be~~ is optionally substituted with phenyl, COOC₁₋₆ alkyl or COC₁₋₆ alkyl,

A ~~means~~ is a straight-chain or branched C₁₋₆ alkylene, straight-chain or branched C₁₋₆ alkenylene or -(CH₂)_p-Q-(CH₂)_q-,

B ~~means~~ is hydrogen or -(CH₂)_p-U,

Q ~~means~~ is C₃₋₇ cycloalkyl, indanyl, 5-, 6- or 7-membered saturated heterocycloalkyl with 1-2 N, O or S atoms, C₆-C₁₀ aryl or 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, which ~~can be~~ is optionally annellated with benzene,

U ~~means~~ is hydrogen, C₁₋₆ alkyl optionally substituted with halogen, C₃₋₇ cycloalkyl, indanyl, C₇₋₁₀ bicycloalkyl, C₆₋₁₀ aryl or 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, which ~~can be~~ is optionally annellated with benzene, whereby wherein the aryl and or heteroaryl radical can be is optionally substituted with halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, CF₃, NO₂, NH₂, N(C₁₋₄ alkyl)₂, cyano, CONH₂, -O-CH₂-O-, -O-(CH₂)₂-O-, SO₂NH₂, OH, phenoxy or COOC₁₋₄ alkyl, ~~or~~

R⁸ and B together with the nitrogen atom optionally form a 5- to 7- membered saturated heterocycle, which ~~can contain~~ optionally contains another oxygen, nitrogen or sulfur atom and ~~can be~~ is optionally substituted with C₁₋₄ alkyl, phenyl, benzyl or benzoyl or form an unsaturated 5-membered heterocycle, which ~~can contain~~ optionally contains 1-3 N atoms and ~~can be~~ is optionally substituted with phenyl, C₁₋₄ alkyl or halogen, ~~or~~

R⁷ and A together with the nitrogen atom optionally form a 5- to 7- membered saturated heterocycle, which ~~can contain~~ optionally contains another oxygen, nitrogen or sulfur atom or forms an unsaturated 5-membered heterocycle, which ~~can contain~~ optionally contains 1-3 N atoms,

m ~~means~~ is 0, 1 or 2,

n and r ~~mean~~ is 0, 1 to 6,

p and q ~~mean~~ is 0 to 6,

R⁹ and R¹⁰ ~~mean~~ is hydrogen or C₁₋₆ alkyl,

R¹¹ ~~means~~ is C₁₋₆ alkyl, -NH₂, -NH-CH₃, -NH-CN, C₆₋₁₀ aryl optionally substituted with halogen, C₁₋₄ alkyl or CF₃, or 5- or 6-membered heteroaryl with 1 to 4 nitrogen, sulfur or oxygen atoms that is optionally substituted with halogen, C₁₋₄ alkyl or CF₃,

R¹² and R¹³ ~~mean~~ are hydrogen, C₁₋₆, alkyl, phenyl optionally substituted with halogen or C₁₋₄ alkyl, benzyl optionally substituted with halogen or C₁₋₄ alkyl, or C₃₋₇ cycloalkyl,

R¹⁴ ~~means~~ is hydrogen, hydroxy, C₁₋₆ alkoxy, phenyl, C₁₋₆ alkyl optionally substituted with CO₂H, CO₂C₁₋₆ alkyl, hydroxy, C₁₋₄ alkoxy, halogen, NR¹⁵R¹⁶, CONR¹²R¹³, ~~or~~ phenyl, or C₂₋₆ alkenyl optionally substituted with phenyl, cyano, CONR¹²R¹³ or CO₂C₁₋₄ alkyl,

R¹⁵ and R¹⁶ ~~mean~~ are hydrogen, C₁₋₆ alkyl, phenyl or benzyl, ~~or~~ and

R¹⁵ and R¹⁶ together with the nitrogen atom optionally form a saturated 5-, 6-, or 7-membered ring, which ~~can~~ optionally contains another nitrogen, oxygen or sulfur atom and ~~can be~~ is optionally substituted with C₁₋₄ alkyl, phenyl, benzyl or benzoyl,

~~whereby~~ wherein

~~if X = O, R⁶ means methyl and R², R³, R⁴ and R⁵ mean hydrogen,~~

R¹ is not 6-((4-aminobenzyl)aminomethyl), 6-((4-dimethylaminobenzyl)aminomethyl), 6-((4-aminobenzyl) (tert-butyloxycarbonyl)aminomethyl), or 6-((4-dimethylaminobenzyl) (tert-butyloxycarbonyl)aminomethyl).

Claims 2-5 have been cancelled.

6. (Twice Amended) ~~Compounds~~ A compound according to claim 1, ~~in which~~ wherein R^1 and R^2 together with two adjacent carbon atoms ~~mean~~ form a 3- to 8-membered ring, ~~preferably 5- to 6-membered ring, which that~~ is substituted with $-(CHR^9)_r-NR^7-A-NR^8B$.

7. (Amended) ~~Compounds~~ A compound according to claim 6, ~~in which~~ wherein $r = 0$.

8. (Twice Amended) ~~Compounds~~ A compound according to claim 1, wherein A ~~means~~ is a straight-chain or branched C_{1-6} alkylene or $-(CH_2)_p-Q-(CH_2)_q-$, ~~and~~ wherein p and q ~~mean~~ are each independently 1-4.

9. (Amended) ~~Compounds~~ A compound according to claim 1, ~~in which~~ wherein U ~~means~~ is hydrogen, alkyl that is optionally substituted with halogen, C_{3-7} cycloalkyl ~~and or~~ optionally substituted phenyl.

10. (Amended) A compound according to claim 1, which is
6-((3-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,

6-(meta-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,

6-(meta-(N-[3-amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,

6-((4-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,

6-(para-(N-[3-amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,

6-(para-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,

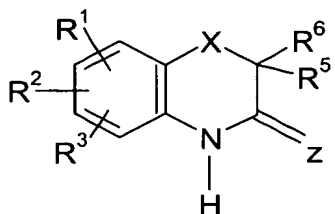
6-((3-aminomethyl-cyclohex-1-yl)-methyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-(3-(N-[3-amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-cyclohex-1-ylmethyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-((omega-aminobutyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-((omega-aminopentyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-((omega-aminohexyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-((3-[4-nitrobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-((3-[2-methylbenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-((3-[2,4-dichlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-((3-[chlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride,
6-((3-[3,4-dichlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride, or
6-((3-benzylaminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride ~~according to claim 1.~~

11. (Twice Amended) ~~Pharmaceutical agent that contains a~~ A pharmaceutical composition comprising a compound according to claim 1 and one or more pharmaceutically ~~common vehicles or adjuvants~~ acceptable auxiliaries.

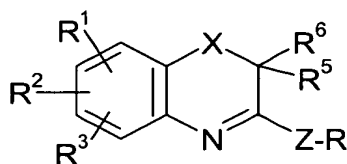
12. (Twice Amended) ~~Use of a compound according to claim 1 for the production of a pharmaceutical agent for treating a disease that is triggered by NOS~~ A method of treating a disease that is triggered by NOS comprising administering to a patient in need thereof a pharmaceutical composition according to claim 11.

13. (Amended) ~~Use according to claim 11 for treatment of~~ A method of treating a neurodegenerative diseases comprising administering to a patient in need thereof a pharmaceutical composition according to claim 11.

14. (Twice Amended) ~~Process A process for the production of~~ preparing a compound of formula I according to claim 1, characterized in that a compound of formula II or its salt comprising reacting a compound of formula IIa or IIb or a salt thereof



IIa

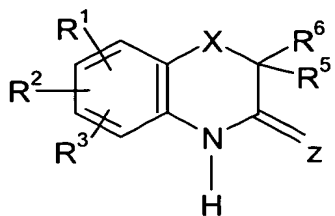


IIb

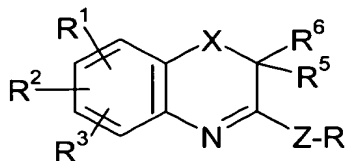
in which wherein

~~R¹, R², R³, R⁵, R⁶ and X have the above mentioned meaning~~ are as defined in claim 1, Z is oxygen or sulfur and R ~~means is~~ is a C₁₋₆ alkyl, ~~is reacted with ammonia or a primary amines, whereby existing amino groups are optionally intermediately protected and optionally then acylated, the isomers are separated or the salts are formed.~~

15. (Amended) ~~Compounds~~ A compound of formulas IIa and or IIb



IIa



IIb

in which wherein

R^1, R^2, R^3, R^5, R^6 and X have the above meaning,

R^1 is $-(CHR^9)_n-NR^7-A-NR^8-B$,

R^2, R^3, R^4 and R^5 are hydrogen,

R^6 is methyl,

X is oxygen or sulfur, and R means is a C_{1-6} alkyl.

Claims 16-18 have been newly added.